The pyrethrins and related compounds. Part XLII:† Structure–activity relationships in fluoro-olefin non-ester pyrethroids

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Abstract: A series of compounds containing fluorine atoms in place of hydrogen in olefinic non-ester pyrethroids has been synthesised using a route based on novel intermediates, ie 2-fluoroallyl acetates, which are coupled with aryl Grignard reagents, and tested against several insect species. In most cases, after introduction of fluorine at the olefinic position, the activity remains high in both the 1-aryl-1-(3-arylprop-2-enyl)cyclopropane and the (1-aryl-4-arylbut-2-enyl)cyclopropane series. In particular, the former series have potential as soil insecticides, because in tests against *Diabrotica balteata*, activities were high, and dose-transferability factors were increased by the introduction of fluorine.

Keywords: pyrethroids; insecticides; synthesis; *Diabrotica balteata*; *Musca domestica*; *Phaedon cochleariae*; fluoro-olefins; structure–activity relationships

1 INTRODUCTION

In a series of papers dealing with non-ester pyrethroids,[1–4] structure–activity relationships showed that the most active compounds conform to the general structure shown in Fig 1. Optimisation within this formula, by us and others (1980–1988), has provided commercially important compounds such as etofenprox,[5] MTI800[6] and NRDC 200.[3] Subsequent developments include silafluofen,[7] flufenprox[8] and F-1327[9] (Fig 1). The spectrum of activity of non-esters is narrower than that of esters, but the combination of high toxicity against rice pests and low fish toxicity has proved important. Within the non-ester structure, more variation is possible in the central region, but less in the alcohol region, if activity is to be retained.

In the area of pyrethroid esters, where investigations have extended to both the alcohol and acid regions, multiply-fluorinated compounds have been shown to be particularly effective as soil insecticides eg tefluthrin,[10] fenfluthrin,[11] and acaricides eg acrinathrin.[12] A single fluorine at position 4 of a 3-phenoxybenzyl moiety improves activity significantly against some species.[13]

We have therefore undertaken an investigation, reported here, of the effect of introducing fluorine into non-ester pyrethroids of four types (**I**–**IV**, Fig 2). These offer the possibility of fluorine substitution in the central region, as well as in the acid and alcohol regions previously examined. The group of compounds related to NRDC 200, where the link is an olefinic unit, appeared particularly attractive because of their increased effectiveness when compared to other link groups.[1–3]

2 EXPERIMENTAL

2.1 Reference compounds

Of the reference compounds tested in the present study, bifenthrin was a gift from FMC, and the remainder (tefluthrin, etofenprox, NRDC 199, NRDC 200, 1-(4-fluorophenyl)-1-(3-(4-fluoro-3-phenoxyphenyl)prop-1-enyl)cyclopropane (compound **31**), 1-(4-trifluoromethoxyphenyl)-1-(3-(3-phenoxyphenyl)prop-1-enyl)cyclopropane (compound **32**), and 1-(4-trifluoromethoxyphenyl)-1-(3-(4-fluoro-3-phenoxyphenyl)prop-1-enyl)cyclopropane (compound **33**) were synthesised as described elsewhere.[4,5,10]

2.2 Synthesis

2.2.1 Spectral data and work-up

The [^{1}H] and [^{13}C]NMR spectra of synthesised compounds were determined on a JEOL GX-400 spectrometer (^{1}H frequency: 400 MHz, ^{13}C frequency: 100 MHz), using 32 and 64 K data points respectively. In all cases, samples were dissolved in deuterochloroform and tetramethylsilane was used as internal standard. In lists of chemical shifts, the order indicated on Fig 3 is followed (ignoring absent or equivalent atoms), and superscripts $^{a,b,\cdots}$ indicate

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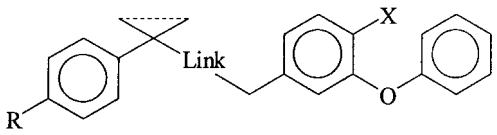


Designation	R	--------	Link	X
Etofenprox	EtO	no bond	CH_2O	H
MTI 800	EtO	no bond	$CH_2.CH_2$	F
NRDC 199	Cl	bond	$CH\overset{E}{=}CH$	F
NRDC 200	EtO	bond	$CH\overset{E}{=}CH$	F

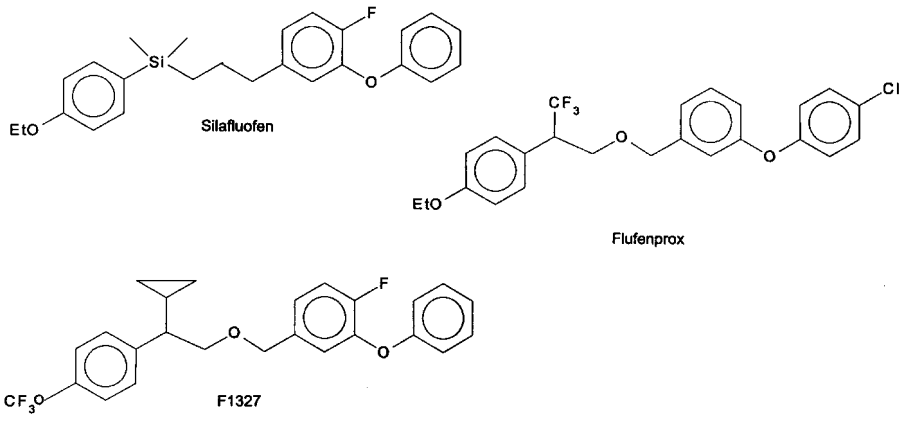


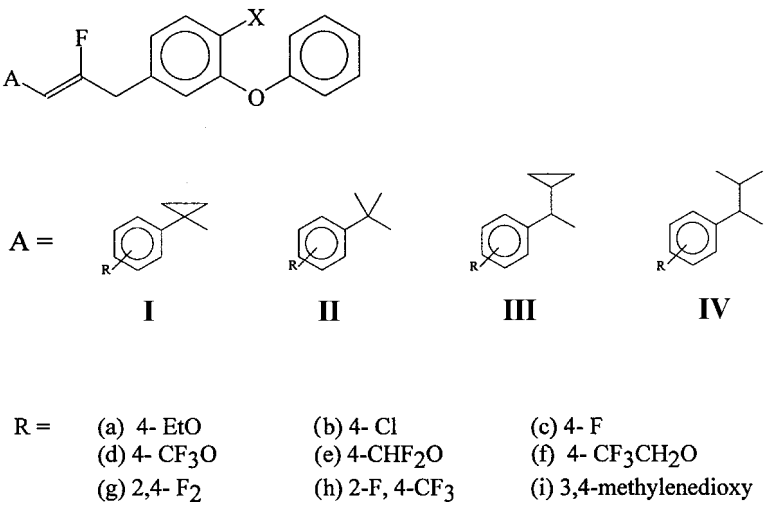
Figure 1. Review of active non-ester pyrethroid structures.

uncertain assignments that may be transposed. Figures in parentheses indicate coupling constants (to fluorine) in Hz. Differences are considered significant if greater than 1 ppm (^{13}C) or 0.1 ppm (^{1}H).

The term 'processed' in descriptions of syntheses implies extraction with diethyl ether (×3), washing the organic layer with water (×2), drying over magnesium sulfate and removing solvent using a rotary evaporator to yield a residue of product.

2.2.2 General

New compounds were synthesised according to the reaction scheme in Fig 4. The reaction to form the 2-fluoro-2-methoxycarbonylvinyl compounds (**I–IV**, X = CO_2Me — see Section 2.2.4) followed the conditions described by Erdik,[14] using zinc and cuprous chloride in acetic anhydride to induce a Reformatsky-type reaction with methyl fluorodichloroacetate. The stereochemistry of the product was established as *Z*



R = (a) 4- EtO (b) 4- Cl (c) 4- F
(d) 4- CF_3O (e) 4-CHF_2O (f) 4- CF_3CH_2O
(g) 2,4- F_2 (h) 2-F, 4-CF_3 (i) 3,4-methylenedioxy

X = H, F

Figure 2. Structures of non-ester pyrethroids synthesised.

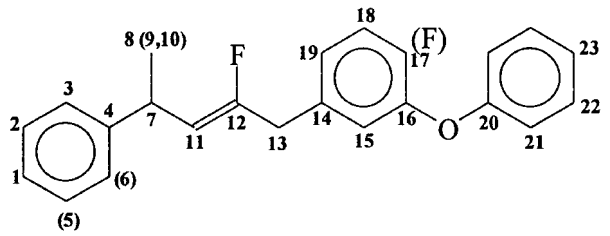


Figure 3. Numbering sequence used for listing NMR shifts.

from the NMR spectra, examined in detail for the Ar=4-chlorophenyl case. In particular, the coupling constant between the olefinic proton (at 6.19) and the fluorine atom was 33 Hz. This falls well within the range of values (32–40 Hz) observed for similarly substituted olefins, when the H and F atoms are known to be mutually *trans*.[15] In confirmation, a small amount of the other product, with the proton at 5.7 ppm, was also isolated. This had a J_{HF} of 18 Hz, within the range (16–22 Hz) observed for *cis*-oriented H, F atoms. Formation of this latter product was much suppressed compared with the alternative method,[16] using $(EtO)_2PO.CHF.CO_2Et$ by which it is formed as the major (up to 95%) product.

The two steps to form the acetates (**I–IV**, X=CH_2OAc) were routine, and subsequent coupling with the 3-phenoxyphenyl Grignard reagent (or its 4-fluoro analogue) was carried out as described for the non-fluorinated olefins.[4]

2.2.3 Aldehydes

The aldehydes used to synthesise compounds **1–30** (see Table 1) were mostly available from previous work, **1,2,5,6,17,18**,[3] **3,4,19–22,29,30**,[2] **7–12,23,24**,[4] **27,28**,[17] except those below which were made by the methods described.[1,3]

1-(2,4-difluorophenyl)-cyclopropanecarboxaldehyde (for compounds **13,14**); [^{1}H]NMR δ 1.39, 1.63 (each m, cyclopropyl), 6.9 (m, ArH-2+ArH-4), 7.19 (dt, 6, 8, ArH-5) 9.01 (d, 1, CHO).

1-(2-fluoro-4-trifluoromethylphenyl)cyclopropanecarboxaldehyde (for compounds **15,16**); [^{1}H]NMR δ 1.44, 1.68 (each m, cyclopropyl), 7.4 (m, 3×ArH), 8.97(s, CHO).

1-cyclopropyl-4-ethoxyphenylacetaldehyde (for compounds **25, 26**); [^{1}H]NMR δ 0.21, 0.34, 0.60, 0.72, 1.28 (each m, cyclopropyl), 2.76 (dd, 3, 10 Hz, H-7), 7.16 and 6.91 (4×Ar-H), 9.70 (d, 2 Hz, CHO), 1.41(t) and 4.03 (q) (OEt).

2.2.4 (2-Fluoro-2-methoxycarbonylvinyl) intermediates (**V**)

Example (*V, A=Ia*). To a stirred mixture of acid-washed zinc powder (4.1 g), copper (I) chloride (0.63 g) and molecular sieve 4A (4.2 g) in dry tetrahydrofuran (72 ml) under nitrogen, 1-(4-ethoxyphenyl)cyclopropanecarboxaldehyde (4.7 g, 25 mmol) was added slowly, followed by acetic anhydride (2.6 ml). After the mixture had been warmed to 50 °C, methyl dichlorofluoroacetate (3.3 g, 23 mmol) was added dropwise, and stirring was continued for 4 h at 50 °C. After cooling, the mixture was diluted with diethyl ether (150 ml), filtered through a bed of Celite, and the filtrate concentrated under reduced pressure. The residual oil was chromatographed on silica gel using diethyl ether+hexane (1+9 by volume) to yield 1-(4-ethoxyphenyl)-1-(2-fluoro-2-methoxycarbonylvinyl)-cyclopropane (3.48 g, 52%). [^{1}H]NMR δ 7.2, 6.8, 1.21, 1.28, 6.23(33), 3.77 (OMe), 1.40, 4.00 (OEt) and [^{13}C]NMR δ 157.7, 114.3, 129.7, 134.9, 22.8, 16.3(3), 125.7(5), 146.8(260), 161.7(35), 52.4 (OMe), 63.4 and 14.4(OEt).

The other compounds made by the same method are listed below. Structure and purity were confirmed in each case by [^{1}H] and [^{13}C]NMR spectroscopy. They all showed peaks at 122.8–128.6 (=CH), 146.5–147.5(255–260) (=CF), 161.2–161.9(35)(CO) and 52.4–52.7 (OMe) (^{13}C) and at 6.00–6.33(33)(=CH) and 3.78–3.83(OMe)(^{1}H). The coupling constant for the =CH ^{13}C peak was characteristic of the structural type, being 33 Hz (type **I**), 6 Hz (type **II**), or 11 Hz (types **III** and **IV**). ^{13}C peaks from the rest of the molecule (atoms 1 to 10, Fig 3) are given separately for each compound in Appendix 1.

2.2.5 (2-Fluoro-3-hydroxyprop-1-enyl) intermediates (**VI**)

Example (*VI, A=Ia*). 1-(4-Ethoxyphenyl)-1-(2-fluoro-2-methoxycarbonylvinyl)cyclopropane (Section 2.2.4; 2.3 g, 8.7 mmol) in dry diethyl ether (10 ml) was added dropwise to a stirred suspension of lithium aluminum

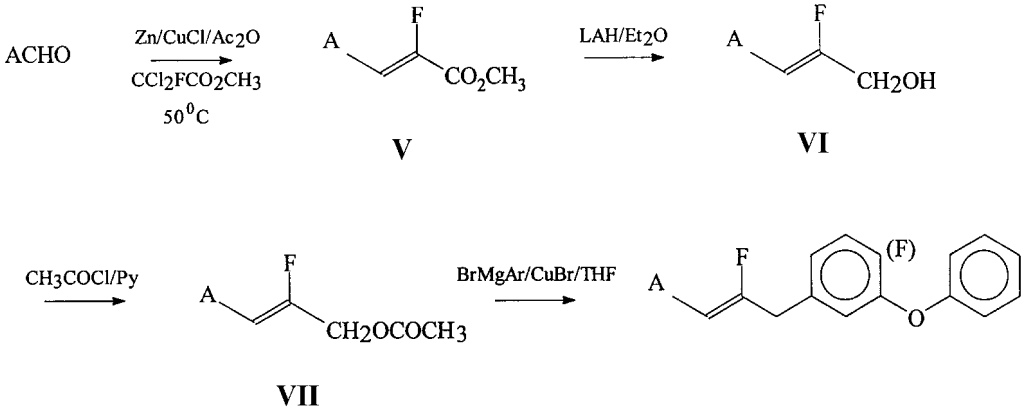


Figure 4. Synthesis scheme.

hydride (0.55 g, 14 mmol) in dry diethyl ether (60 ml) at 0 °C. Stirring was continued during 1 h, while the mixture warmed to room temperature. Water (10 ml) was added, and the mixture was processed. The residual oil was chromatographed on silica gel using diethyl ether + hexane (2 + 3 by volume) to yield 1-(4-ethoxyphenyl)-1-(2-fluoro-3-hydroxyprop-1-enyl)cyclopropane (1.51 g, 74%). [^{1}H]NMR δ 6.8, 7.2, 1.1, 5.10(37), 4.04(16), 2.0(OH) and 3.99, 1.39(OEt), and [^{13}C]NMR δ 157.2, 114.2, 128.8, 136.7, 20.6(2), 15.4(3), 112.2(9), 158.0(260), 61.6(32), 63.4 and 14.9(OEt).

The other compounds made by the same method are listed below. Structure and purity were confirmed in each case by [^{1}H] and [^{13}C]NMR spectroscopy. They all showed the expected peaks from the aromatic region (where the only significant difference from the methoxycarbonyl compound (Section 2.2.3) was for C-4 (*c*1.8 ppm larger in the but-2-enol)) and peaks at 109.9–112.2 (types **I, III, IV**, J_{CF} = 9,14,13 respectively) or 116.0–116.7(8) (type **II**) (=CH), 156.4–158.8(255–263)(=CF), and 61.0–62.0(33–37)(CH_2) (^{13}C); and at 4.98–5.12(36–41)(=CH), 3.95–4.14(15)(CH_2) and 1.7–3.3(OH)(^{1}H). ^{13}C peaks from the alkyl/cycloalkyl region for the other intermediates are given in Appendix 2.

2.2.6 (3-Acetoxy-2-fluoroprop-1-enyl) intermediates (**VII**)
Example (*VII, A = Ia*). Acetyl chloride (2 ml) was added slowly to a stirred solution of 1-(4-ethoxyphenyl)-1-(2-fluoro-3-hydroxyprop-1-enyl)cyclopropane (0.99 g, 4.2 mmol) (Section 2.2.5) in benzene (50 ml) and pyridine (0.38 ml) at 0 °C and stirring was continued for 24 h while the mixture warmed to room temperature. Water (10 ml) was added after cooling to −78 °C, and the mixture was processed. The residual oil was chromatographed on silica gel using diethyl ether + hexane (1 + 4 by volume) to yield 1-(4-ethoxyphenyl)-1-(3-acetoxy-2-fluoroprop-1-enyl)cyclopropane (1.16 g, 99%).

The other alcohols from Section 2.2.5 were acetylated similarly in essentially quantitative yield. In each case, structure and purity were confirmed by [^{1}H] and [^{13}C]NMR spectra, which were the same as for the alcohols (Section 2.2.5) except for the following significant differences: new peaks at 2.07–2.11 (^{1}H) and 170.4, 20.8 (^{13}C):($COCH_3$); shifts for C-13 of *c* 0.5 ppm (^{1}H) and *c*1.2 ppm (^{13}C) and of *c* + 4 ppm and *c* − 4 ppm for C-11 and C-12 respectively.

2.2.7 Synthesis of final products (**1–28**, *Table 1*)
Example (*3*). A Grignard reagent prepared from 3-phenoxybromobenzene[18] (0.29 g, 1.2 mmol) in dry tetrahydrofuran (2 ml) and magnesium (28 mg, 1.2 mmol) under nitrogen using iodine as initiator at *c*40 °C for 10 min was cooled to −78 °C. Copper (I) bromide (20 mg) was added, followed by a solution of 1-(4-chlorophenyl)-1-(3-acetoxy-2-fluoroprop-1-enyl)cyclopropane (0.14 g, 0.5 mmol, Section 2.2.7) in tetrahydrofuran (5 ml) (slowly with stirring). The mixture was allowed to warm to room temperature overnight, water (2 ml) was added and the mixture was processed. The residual oil was purified by preparative thin-layer chromatography (solvent: diethyl ether + hexane, 1 + 9 by volume) and then preparative high performance liquid chromatography (column: C18; solvent: methanol; flow rate: 8 ml min^{-1}) to afford 1-(4-chlorophenyl)-1-(2-fluoro-3-(3-phenoxyphenyl)prop-1-enyl)cyclopropane (65 mg, 33%). [^{13}C]NMR δ 131.4, 128.5, 128.2, 143.6(1), 16.3(3), 20.6(2), 110.6(10), 38.6(28), 138.2, 123.6, 129.8, 117.2, 157.0[a], 119.1, 157.4[a], 118.9, 129.8, 123.3.

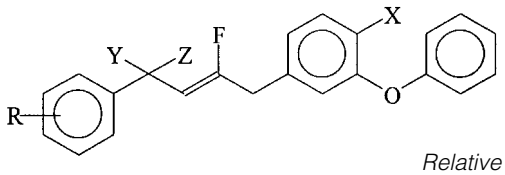
Other acetates (from Section 2.2.6) were similarly reacted to give the 14 other compounds (the odd-numbered ones in Table 1) in similar yields. All were characterised for structure and purity by [^{1}H] and [^{13}C]NMR spectroscopy. None of the ^{13}C chemical shifts of atoms 1–10 (Fig 3) was significantly different from those in the acetates (Section 2.2.6). Those for C-11 were *c*4 ppm less, for C-12 *c*5 ppm larger, and for C-13 to C-23 were in the following ranges: 37.8–38.7(28), 138.1–138.5, 123.6–124.0, 129.7–129.9, 117.1–117.3, 157.0–157.1[a], 119.1–119.2, 157.4–157.5[a], 118.9, 129.7–129.8, 123.3–123.4.

Example of method (*4*). Similarly, a Grignard reagent prepared from 4-fluoro-3-phenoxybromobenzene[4] (3.56 g, 13 mmol) was reacted with 1-(4-chlorophenyl)-1-(3-acetoxy-2-fluoroprop-1-enyl)cyclopropane (2.95 g, 11 mmol). The product, 1-(4-chlorophenyl)-1(2-fluoro-3-(4-fluoro-3-phenoxyphenyl)prop-1-enyl)cyclopropane (2.2 g, 50%) was isolated; [^{13}C]NMR δ 131.5, 128.3, 128.6, 143.5(1), 16.2(3), 20.6(2), 110.8(10), 159.4(261), 38.1(28), 136.7(4), 124.8(7), 117.0(18), 153.2(248), 143.6(11), 121.9, 157.2, 117.2, 129.8, 123.3.

Other acetates (from Section 2.2.6) were similarly reacted to give the 14 other compounds (the even-numbered ones in Table 1) in similar yields. All were characterised for structure and purity by [^{1}H] and [^{13}C]NMR spectroscopy. The chemical shifts of atoms 1 to 13 were not significantly different from those for the 4-H compounds, and those for C-14 to C-23 were as follows: 133.1–136.7(3–5), 124.8(6–7), 117.0–117.2(18), 153.1–153.3(248), 143.5–143.7(11), 121.8–121.9, 157.2–157.4, 117.2–117.4, 129.7–129.8, 123.2–123.3.

2.3 Biological testing

2.3.1 Houseflies (*Musca domestica L*)
Female flies were treated on the thorax with a drop (1 μl) of an acetone solution of the insecticide using a micro-applicator. Two replicates of 15 flies were used at each dose rate, and six dose rates were used per compound. After treatment, the flies were maintained at 20 °C, and kill was assessed after 48 h. LD_{50} values were calculated using the Polo-PC programme (LeOra Software Inc, USA) and potencies relative to bioresmethrin were calculated from the inverse ratios of the LD_{50} values.



Compound	R	X	Relative activity[a] *M domestica*	*P cochleariae*
*Type **I** (Y,Z=(CH$_2$)$_2$)*				
1	4-OEt	H	40	53
2	4-OEt	F	33	120
3	4-Cl	H	28	28
4	4-Cl	F	54	71
5	4-F	H	50	6.6
6	4-F	F	77	*c* 70
7	4-OCF$_3$	H	–	25
8	4-OCF$_3$	F	–	39
9	4-OCHF$_2$	H	26	15
10	4-OCHF$_2$	F	25	64
11	4-OCH$_2$CF$_3$	H	14	20
12	4-OCH$_2$CF$_3$	F	22	130
13	2,4-F$_2$	H	c.15	3.3
14	2,4-F$_2$	F	c 85	10
15	2-F, 4-CF$_3$	H	c 5	2.9
16	2-F, 4-CF$_3$	F	–	150
17	3,4-CH$_2$O$_2$	H	–	28
18	3,4-CH$_2$O$_2$	F	100	94
*Type **II** (Y,Z=(CH$_3$)$_2$)*				
19	4-OEt	H	25	4.7
20	4-OEt	F	40	24
21	4-Cl	H	9.5	1.6
22	4-Cl	F	11	5.2
23	4-OCF$_3$	H	16	13
24	4-OCF$_3$	F	13	29
*Type **III** (Y=H, Z=Cyclopropyl)*				
25	4-OEt	H	9.5	40
26	4-OEt	F	59	160
27	4-Cl	H	48	23
28	4-Cl	F	c 10	*c* 70
*Type **IV** (Y=H, Z=Isopropyl)*				
29	4-Cl	H	<1	<1
30	4-Cl	F	12	*c* 1
NRDC 199			70	82
NDRC 200			100	160

Table 1. Activity of compounds examined against *Musca domestica* and *Phaedon cochleariae*

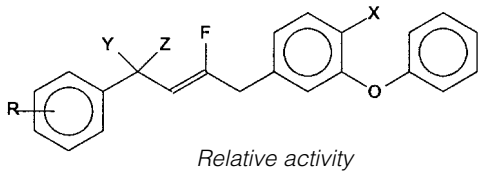
[a] Figures given are activities relative to bioresmethrin (=100).

2.3.2 Mustard beetles (Phaedon cochleariae Fab)
Similarly, acetone solutions of test compounds were applied ventrally to adult mustard beetles, and kill was assessed after 48 h. Two replicates of 20 beetles were used at each dose level, and five dose levels were used for each compound. LD_{50} values and relative potencies were calculated as for houseflies.

2.3.3 Corn rootworm (Diabrotica balteata Lec)
For topical assays, late-instar larvae were treated with drops (1 µl) of the insecticide in methyl ethyl ketone, using three replicates of 10 larvae at each dose, and five dose rates per compound. Kill was assessed after 48 h at 20 °C. LD_{50} values and relative potencies were calculated as above.

For residual soil activity tests, a known quantity of the compound dissolved in acetone (1.0 ml) was applied evenly to sandy soil (22 g) with a 10% moisture content, in a Petri dish. One hour later, 10 larvae were introduced, then, after a further 48 h at 20 °C, mortality was assessed. Two replicates of 10 larvae were used at each dose level, and five dose levels were used for each compound. The LC_{50} values were calculated as above as concentrations (in mg kg^{-1}) of the compound in the soil.

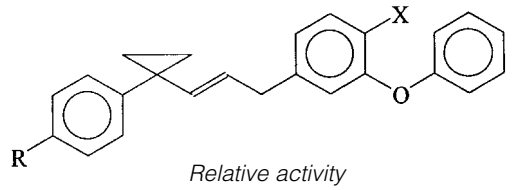
2.3.4 Mites (Tetranychus urticae Koch)
Adult mites from a susceptible strain (GSS) were immersed in a solution (35 µl) of the test compound in acetone + water (1 + 4 by volume) for 30 s. Kill was



Compound	R	X	Relative activity: Contact[a]	Relative activity: Soil[b]	Dose transferability[c]
*Type **I** (Y,Z=(CH$_2$)$_2$)*					
1	4-OEt	H	130	83	44
2	4-OEt	F	73	48	66
3	4-Cl	H	92	77	84
5	4-F	H	210	83	39
6	4-F	F	79	100	130
7	4-OCF$_3$	H	150	63	42
8	4-OCF$_3$	F	18	38	210
9	4-OCHF$_2$	H	24	44	180
10	4-OCHF$_2$	F	30	73	240
14	2,4-F$_2$	F	110	20	18
15	2-F, 4-CF$_3$	H	33	80	240
16	2-F, 4-CF$_3$	F	140	110	79
17	3,4-CH$_2$O$_2$	H	77	59	77
18	3,4-CH$_2$O$_2$	F	61	46	75
*Type **II** (Y,Z=(CH$_3$)$_2$)*					
19	4-OEt	H	66	8	12
20	4-OEt	F	25	–	–
21	4-Cl	H	80	14	18
22	4-Cl	F	100	120	120
23	4-OCF$_3$	H	6	–	–
24	4-OCF$_3$	F	25	65	260
*Type **III** (Y=H, Z=Cyclopropyl)*					
25	4-OEt	H	14	3.8	27
26	4-OEt	F	41	9.6	23
27	4-Cl	H	37	8.9	24
28	4-Cl	F	66	33	50
*Type **IV** (Y=H, Z=Isopropyl)*					
29	4-Cl	H	17	7.3	43
30	4-Cl	F	33	6.9	21

[a] Activity relative to tefluthrin = 100 (LD_{50} = 0.003 μg per insect).
[b] Activity relative to tefluthrin = 100 (LC_{50} = 0.024 mg kg^{-1}).
[c] (soil activity) × 100/(contact activity).

Table 2. Activity of new compounds against *Diabrotica balteata*



Compound	R	X	Relative activity: Contact[a]	Relative activity: Soil[b]	Dose transferability[c]
NRDC 199	Cl	F	22	3.5	16
NRDC 200	EtO	F	39	5.6	14
31	F	F	160	40	25
32	CF$_3$O	H	150	40	27
33	CF$_3$O	F	85	83	98
Tefluthrin			100	100	100
Fenfluthrin			200	120	55
Etofenprox			65	<2	<3

[a] Activity relative to tefluthrin = 100 (LD_{50} = 0.003 μg per insect).
[b] Activity relative to tefluthrin = 100 (LC_{50} = 0.024 mg kg^{-1}).
[c] (soil activity) × 100/(contact activity).

Table 3. Activity of reference compounds against *Diabrotica balteata*

assessed after 72h at 21 °C, when mites exhibiting repetitive (non-reflex) movement of more than one locomotory appendage were considered alive. Three replicates of 25 mites were used at each dose rate, and five or six dose rates were used per compound.

3 RESULTS AND DISCUSSION

The results for all 30 compounds against houseflies and mustard beetles are given in Table 1. The activities against these species, which have been used at Rothamsted for many years for discerning structure–activity relationships (SARs) in pyrethroids, are generally high. Compared with the simpler compounds[3] (including NRDC 199 and NRDC 200) in which the central olefinic bond does not bear a fluorine substituent, activities are generally of the same order, as assessed by statistical analysis using a logarithmic scale (cf the data analysis method used previously[19]). For mustard beetles, the mean value for H to F change was 0.887 with a standard error of $\times/\div$ 1.25 for 12 data points. For houseflies the corresponding value for 14 data points was 0.634 with a standard error of $\times/\div$ 1.29.

In addition, the SARs identified previously[1–3] for non-fluorinated non-ester pyrethroids are paralleled in the present series, so that cyclopropyl and alkene combination (type **I**) remains particularly effective and a 4-F substituent increases activity against mustard beetles. These SARs also apply to compounds in which the gem-dimethyl/cyclopropyl group is not part of the central backbone (compounds **25** to **30**, structural types **III** and **IV**), but constitutes a branch from it.

To extend the study to commercially important species, the activities of the synthesised compounds were also determined against a species of mite (*T urticae*) and a soil pest (*D balteata*).

Although miticidal activity in some non-ester pyrethroids has been reported,[20] to date, only ester pyrethroids (eg bifenthrin and acrinathrin) have been developed as miticides. Of the eight non-esters tested against *T urticae* (compounds **1, 2, 10, 13, 14, 17, 25, 29**) all had low activity (LC_{50} values greater than 350 mg kg^{-1}), so this aspect was not explored further.

Against the soil pest, *D balteata*, LD_{50} values in topical assays were measured for the present compounds (see Table 2) and some earlier non-fluorinated olefins, a representative non-ester (etofenprox) and two pyrethroidal esters (see Table 3). They all showed good intrinsic activity, in some cases rivalling that of a commercial pyrethroidal soil insecticide, tefluthrin. However, no SARs were discernible except that the generally lower activity of type **IV** compounds (**29** and **30**) against mustard beetles was also observed here.

Results of soil tests are also included in Tables 2 and 3. Here, in addition to intrinsic activity, some other properties of the test compounds (eg volatility, lipophilicity, stability) are known to have added significance.[21] An additional parameter, designated 'dose transferability' (calculated as (relative soil activity)/(relative contact activity) $\times$ 100) provides an assessment of the contributions of these factors. In contrast to results in the topical tests, the soil tests showed compounds of type **I** to have significantly greater activity than those of the other types (**II, III** and **IV**). Further, their dose-transferabilities were higher (mean of factor = 2.95 $\times/\div$ 1.26) than those of the corresponding unfluorinated olefins (direct comparisons could be made for four pairs of compounds, ie NRDC 200/**2, 31/6, 32/7**, and **33/8**). Introduction of an additional fluorine in type **I** compounds (Fig 2, X = H) at another site (the 4-position of the benzyl moiety) has a smaller effect on dose transferability (mean of factor = 1.46 $\times/\div$ 1.59, $n = 10$). The much larger effect of introducing fluorine on the double bond over introducing it at the 4-position of the benzylic moiety must involve some subtle effect (not yet fully understood) because an H to F change in whatever part of the molecule would influence physical properties equally.

In conclusion, many of the fluorinated compounds with the combination of features represented in structure **I** compare well as soil insecticides with tefluthrin, a commercial ester pyrethroid, in contrast to earlier non-ester pyrethroids, eg etofenprox, NRDC 199 and NRDC 200.

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Appendix 1: [^{13}C]NMR peaks for intermediates (**I–IV**, X=CO_2Me)

Compound	*[^{13}C]NMR peaks*
Ib	132.5, 128.5, 130.1, 141.4(1), 22.8, 16.6(3).
Ic	161.6(245), 115.1(21), 130.3(8), 138.6(1,1), 22.9, 16.4(4)
Id	147.9(2), 120.9, 129.7, 141.6(1), 22.8, 16.5(4) and 120.4 (257) (CF_3)
Ie	149.9(3), 119.5, 130.0, 140.1, 22.8, 16.5(4) and 116.0(260) ($OCHF_2$)
If	156.2, 114.8, 130.0, 137.1, 22.8, 16.4(4) and 65.9(36), 123.3(278) (OCH_2CF_3)
Ig	162.1[a](248,12), 103.8(26,26), 162.0[a](250,12), 125.6(2,12), 131.8(5,9), 110.8(21,4), 18.6(1), 15.9
Ih	131.3(8,33), 112.8(25,4), 162.1(250), 133.6(14), 131.6(4), 120.8(4), 19.0(1), 15.9 and 123.2(275,3) (CF_3).
Ii	146.3[a], 147.4[a], 109.4, 136.8, 121.9, 108.0, 23.4, 16.3(3), and 101.0 (CH_2O).
IIa	157.4, 114.3, 126.7, 141.5(1), 39.0(2), 29.2(2) and 63.4, 14.9 (OEt)
IIb	132.2, 128.5, 127.1, 146.2, 39.2(2), 29.1(3)
IIc	147.0(2), 120.9, 127.2, 146.3, 39.3(2), 29.3(4) and 120.5(256) (CF_3O)
IIIa	157.9, 114.6, 128.4, 133.8, 16.1, 44.3, 4.1, 4.6 and 63.4, 14.9 (OEt)
IIIb	132.7, 128.8, 128.8, 140.5, 15.9(2), 44.5(2), 4.2, 4.6
IVb	132.5, 128.8, 129.8, 140.3, 33.3, 48.2, 20.7, 20.4

Appendix 2: [^{13}C]NMR peaks for the alkyl/cycloalkyl region in intermediates (**I–IV**, X=CH_2OH)

Compound	*[^{13}C]NMR peaks*
Ib	20.6(2), 16.1(3)
Ic	20.7(2), 15.2(2)
Id	20.7(2), 16.0(4)
Ie	20.7, 15.8(1)
If	20.6, 15.6(3)
Ig	17.0, 14.2(1)
Ih	17.4, 14.2
Ii	21.3(1), 15.5
IIa	38.1, 30.0(4)
IIb	38.4, 29.9(3)
IIc	38.4, 29.9(3)
IIIa	43.3(4), 16.7, 4.5, 4.0
IIIb	43.6(4), 16.5(2), 4.5, 4.1
IVb	47.2(3), 33.4, 20.8, 20.3